Egypt. J. Chem. **Vol. 68**, No. 8 pp. 397 - 413 (2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Efficacy of Cinnamon Extract in Mitigating the Hepato-Renal Toxicity Influenced by Bisphenol A

Alaa H. Dahham[1], Samir M. El Rayes[1*], Nadia A. El-Fahla[2], Heba M.A. Abdelrazek[3]

[1]*Department of Chemistry, Faculty of Sciences, Suez Canal University, Ismailia, 41522, Egypt*

[2]*Department of Zoology, Faculty of Sciences, Suez Canal University, Ismailia, 41522, Egypt*

[3]*Department of Physiology, Faculty of Veterinary Medicine, Suez Canal University, Ismailia, 41522, Egypt*

Abstract

This study explored the ameliorative influence of cinnamon aqueous extract (CIN) in counteracting bisphenol A's (BPA) toxic and negative effects on male *Albino* rats. The male rats (n = 24) were allocated into 4 groups, each with 6 rats. The first group administered distilled water and corn oil, the 2nd group administered cinnamon extract 400 mg/kg (20% v/v in distilled water), the 3rd group received 10 mg BPA /kg (1% w/v in corn oil), and the 4th group was given both BPA and cinnamon extract daily for 3 months. The gain in body weight, homeostasis model assessment–estimated insulin resistance (HOMA-IR), oral glucose tolerance test (OGTT), leptin, resistin, adiponectin, thyroid hormones T3 and T4, lipid profile, albumin, total protein, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were assessed, Moreover, antioxidant capacity (TAC), interleukin-1 beta (IL-1β), malondialdehyde (MDA), creatinine, urea, uric acid, hematological examination; the hemoglobin, RBCs count, hematocrit, erythrocyte indices, total leucocytic count and differential leucocytic count were assayed. Also, liver and kidney tissues were undergoing histopathological investigations. BPA-treated rats showed significant increases in the OGTT, leptin, resistin, T3, AST, ALT, IL-1β, MDA, TC, TG, urea, uric acid, and creatinine. While significant reduction happened with BPA-treated rats in the adiponectin, total protein, TAC, albumin, and HDL. However, there are no significant differences in body weight, HOMO-IR, Insulin, T4, and all hematological indices. The BPA-induced injury of renal and hepatic tissues. Improved metabolic parameters and histopathological retrogressive deviations were detected in rats with co-administered CIN and BPA. Adding CIN enhances and mitigates the negative influences of BPA on metabolism via CIN antioxidant properties and other positive characterization by different mechanisms.

Keywords: cinnamon; BPA; OGTT; IL-1β; leptin; thyroid hormones; antioxidant; histopathology.

1. Introduction

Bisphenol A, (2,2-bis (4-hydroxyphenyl) propane, BPA) is mostly implemented as a monomer to create unsaturated polyester-styrene resins, flame retardants, and polycarbonate (PC) and epoxy resins [1]. It has been established that BPA functions as an endocrine disruptor (ED), having significant biological toxicity and estrogenic effects on living things [2]. Additionally, numerous studies have documented BPA escape from PC food vessels, drinking water tanks made of epoxy resin, and baby bottles [3-5]. Researches have confirmed that endocrine system problems, including heart disease, type 2 diabetes, and others, are strongly interrelated with BPA levels [6]. The livers of male rats that were administered BPA at low doses display oxidative stress [7]. Moreover, the liver is the principle organ in humans and mammals that is accountable for the metabolism of BPA [8].

Natural substances derived from herbs cure sicknesses in traditional regional or local medicine [9]. Bio-friendly relatively safe, eco-friendly and cost-effective herbal medications have stirred from the peripheral to the center with promoted investigations in the traditional medicine arena [10]. In the 21st century, larger statistics of people pursue safe approaches and remedies to healthcare, therefore, herbs are attaining importance in healthcare sector. The request for herbal health products, herbal medicines, nutraceuticals, herbal pharmaceuticals, herbal, cosmetics, food supplements etc., are growing globally owing to their wide range of safety with neglectable side effects, improved compatibility with normal flora, and accessibility at inexpensive prices [11].

Cinnamon, *Cinnamon zeylanicum* from the Lauraceae family, traditional herbal medicine has utilized cinnamon to treat various medical illnesses Gruenwald et al. (2010). It has gained popularity as a natural product due to theories that it provides health benefits, including the capacity to decline sugar levels in blood and serum lipids. It has been hypothesized that cinnamon's active ingredient, cinnamaldehyde, is responsible for the way the spice affects blood glucose [12], Cinnamaldehyde's insulin endorsing effects have initially been explored, and they are believed to be accountable for promoting insulin production, improving insulin sensitivity, and improving clearance of insulin [13], Cinnamon is mostly composed of various essential oils and numerous derivatives, including cinnamaldehyde, cinnamic acid, and cinnamate, all of which are crucial to the spice's natural antioxidant properties[14], anti-inflammation[15], antidiabetic[16], antimicrobial[17,18], anticancer[19, 20], and cholesterol- lipid-lowering characteristics[21-23].

This research aimed to evaluate the potential influence of CIN aqueous extract in ameliorating the negative influence of BPA on insulin sensitivity and hepatorenal toxic effect in male Wistar rats

*Corresponding author e-mail: samir_elrayes@yahoo.com (Samir M. El Rayes).

Received Date: 22 November 2024, Revised Date: 23 December 2024, Accepted Date: 06 January 2025

DOI: 10.21608/EJCHEM.2025.338234.10855

2. Experimental (Materials and Methods)

2.1. Plant material and extraction

Cinnamon zeylanicum bark was bought from Ismailia local market, Egypt. Cinnamon was examined in the Department of Botany, Faculty of Science, Suez Canal University, Ismailia, Egypt. For preparation of cinnamon aqueous extract, the dried cinnamon barks were crinkled into powder and then stowed until used. The aqueous extract of cinnamon was equipped by rinsing 200 g of the dry fine powder in (1000 mL) of warm distilled water (40–50 °C) with shaking every day for 48 hours. Filtration was performed to the later contents through double gauze layers to get cinnamon aqueous extract of 20% that was kept in refrigerator storage until using [24].

2.2. Experimental Animals

Twenty-four male rats (179–219 g; 5–6 months) of Albino type were bought from the Laboratory Animal House, Faculty of Science, Ain Shams University, Egypt. Experimental animals were supplied with ordinary rodents' diet *ad libitum* and tap water. They were maintained in plastic cages and housed with standardized housing conditions in a ventilated room subjected to natural light/dark rhythm, temperature (22 - 25 C°), and 47% ± 2 humidity. They were kept for 14 days for acclimatization prior to the experiment. This study was accomplished in accordance to the ethics guidelines for animal use in the laboratory at the Faculty of Science (REC59/2022), Suez Canal University, Egypt.

2.3. Experimental protocol

Experimental animals were split randomly into 4 groups, six rats each. The first group was given distilled water and corn oil as vehicles and served as the control group. The second group was given 400 mg/kg (20% v/v in distilled water) of cinnamon aqueous extract daily via gavage [24]. The 3rd group received 10 mg/kg (1% w/v in corn oil) of BPA (Sigma-Aldrich Co., USA) daily via gavage [25]. The fourth group administered both BPA 10 mg/kg B.wt. and an aqueous extract of cinnamon 400 mg/kg B.wt. The treatment continued for three months.

2.4. Body and organs weight

Experimental animals' weights were documented at the commencement and then at the termination of the experiment. The increase in body weight was computed as follow: final body weight - starting weight. The relative organ weights were calculated by this rule: absolute weight of the organ or fat mass at the termination of the experiment / body weight at the experiment terminal × 100.

2.5. Oral glucose tolerance test (OGTT)

After overnight fasting, tail vein blood samples were drawn, and the levels of the glucose in the blood were measured using an Accu-Chek Active Co., (Germany) glucometer. Following this, the rats were given 1 g/kg of (40%) oral glucose solution through gavage [26]. The levels of glucose were measured via the glucometer at 0, 15, 30, 60, 90, 120, 150, and 180 minutes intervals.

2.6. Tissue and blood samples collection

At the termination of the experimental duration, male rats were subjected to anesthesia via tetrahydrofuran inhalation. Retroorbital blood samples were. Two samples for each rat were obtained; the first one was collected in plain tubes and left for clotting and further serum separation. The second one was collected in EDTA tubs for further hematological examination. The hemoglobin, RBC count, hematocrit, erythrocyte indices, total leucocytic count and differential leucocytic count were done according to Hoffman, et al. [27]. Sera were harvested and stored at −80°C and implemented for further biochemical, antioxidant enzymes, and lipid peroxidation estimation. The kidneys and liver of each rat were immediately enucleated, blotted with filter paper, and then weighed. A portion of the liver and kidney/ rat were kept in 10% neutral formalin for histopathology. The Sublembur and epididymal fats were dissected and weight their relative weights were determined. Parts of Sublembur and epididymal fats were submerged in 10 % neutral formalin for the histopathology.

2.7. Biochemical parameters

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were estimated spectrophotometrically using (Gallenkamp® and Sons Ltd.; England) photoelectric colorimeter in accordance with Toro and Ackermann [28]; Duncan, et al.[29], Urea, uric acid, and creatinine in sera were measured spectrophotometrically using automatic analyzer according to Jaffe reaction as described by Greenwald [30]. lipid profile calorimetric kits were attained from Diamond Diagnostic Co., Egypt. The total cholesterol (TC) was measured following Allain, et al. [31], while triglyceride (TG) and High-density lipoprotein cholesterol (HDL-C) were done following Fossati and Prencipe [32] and Rifai, et al. [33], respectively.

2.8. Malondialdehyde (MDA) and total antioxidant capacity (TAC)

Serum TAC was measured according to the producer's instructions (Labor Diagnostika Nord GmbH & Co. KG Co., Germany) [34]. MDA levels were determined spectrophotometrically at 535 nm using a UV-VIS spectrophotometer (Hitachi, Japan).

2.9. HOMA-IR calculation

following the manufacturer's procedures, insulin was measured in the blood via Abnova Co., (Germany) ELISA kit. The following formula was used to determine homeostasis model assessment-estimated insulin resistance (HOMA-IR): HOMA-IR = fasting insulin (U/L) x fasting glucose (mg/dL)/ 405, according to Matthews, et al. [35].

2.10. IL-1β, T3 and T4

Specific ELISA kits (Kamiya Biomedical Co., USA) of cat. no. KT-59938, KT-59940, and KT-18885 were used to measure levels of free tetraiodothyronine (T4), triiodothyronine (T3), and interleukin-1 beta (IL-1β) in sera. T3 and T4 ELISA kits had a detection limit of 1 pg/mL, whereas IL-1β had a detection limit of 4.2 pg/mL. The techniques of the former analyses were carried out following the manufacturer's specifications.

2.11. Leptin and resistin assay

Following the manufacturer's protocol, leptin and resistin levels were determined in sera using a specific ELISA (cat. no. KT-437, Kamiya Biomedical Co., USA) and (cat. no. RD391016200R, Biovendor Co., Czech Republic). Resistin and leptin ELISA kits had low detection limits of 0.05 ng/mL and 312.5 pg/mL, respectively.

2.12. Histological assessment

Kidney and liver tissue samples from various rat groups were subjected to fixation in the 10% neutral formalin buffer solution, then 70% and 100% ethyl alcohol were added after specimens were rinsed in tap water the next day. Samples were rinsed in xylene for transparency and immersed in paraffin for 24 hours at 60 °C; paraffin blocks were sliced into 4-5 µm thickness using a sled microtome. After deparaffinization of tissue sections, they were stained with hematoxylin and eosin then assessed for histological analysis using a light microscope [36].

2.13. Statistical analysis

One-way analysis of variance (ANOVA) was implemented to investigate the variations among groups. Post hoc Tukey's test was implemented for inter-group comparisons using GraphPad Prism (Version 5.01, San Diego, USA). The significance was considered when $P \leq 0.05$ among different groups.

3. Results

3.1. Body and organs weight

The experimental rats' weight gain and final body weight were non-significantly changed between the control and other groups. Furthermore, absolute epididymal fat mass, absolute sublumbar fat mass, relative epididymal fat mass, and relative sublumbar fat masses were promoted ($P \leq 0.05$) in BPA-managed rats in comparison to the control ones. While CIN + BPA resulted in a statistical ($P \leq 0.05$) reduction in absolute epididymal fat mass, absolute sublumbar fat mass, relative epididymal fat mass, and relative sublumbar fat mass as matched to the BPA rats **(Table 1)**.

Table 1: Effect of oral CIN administration on body weight gain, epididymal fat, and sub lumbar fat masses fat masses of BPA-intoxicated male *Wistar* rats for three months. Values are represented as mean ± SE *(n=24).*

	Control	CIN (400 mg/ kg)	BPA (10 mg/ kg)	BPA (10 mg/ kg) + CIN (400 mg/ kg)
Initial body weight (g)	169.00 ± 5.74	164.75 ± 6.26	169.25 ± 3.25	167.50 ± 5.63
Final body weight (g)	321.75 ± 13.06	347.75 ± 15.92	335.00 ± 9.70	324.25 ± 22.28
Final body weight gain (g)	152.75 ± 14.36	183.00 ± 10.68	165.7 ± 7.12	156.75 ± 27.83
Absolute epididymal fat mass (g)	3.47 ± 0.25^{b}	3.86 ± 0.63^{b}	6.23 ± 0.42^{a}	3.22 ± 0.41^{b}
Absolute sublumbar fat mass (g)	5.11 ± 0.78^{b}	4.69 ± 0.43^{b}	9.98 ± 0.28^{a}	5.71 ± 0.43^{b}
Relative epididymal fat mass (g %)	1.08 ± 0.06^{b}	1.10 ± 0.15^{b}	1.86 ± 0.12^{a}	1.01 ± 0.16^{b}
Relative sublumbar fat mass (g %)	1.62 ± 0.30^{b}	1.37 ± 0.18^{b}	2.98 ± 0.06^{a}	1.76 ± 0.09^{b}

Superscript letters (a, b, c, d) within the same row refer to significance at $P < 0.05$.

3.2. OGTT

Rat group administrated with BPA demonstrated statistically ($P \leq 0.05$) elevated levels of glucose at 30, 120, and 150 minutes in comparison to the control group. While administration of CIN with BPA statistically ($P \leq 0.05$) mitigated the increased the blood glucose levels at 30, 120, and 150 min as matched with the BPA intoxicated group (Fig. 1)

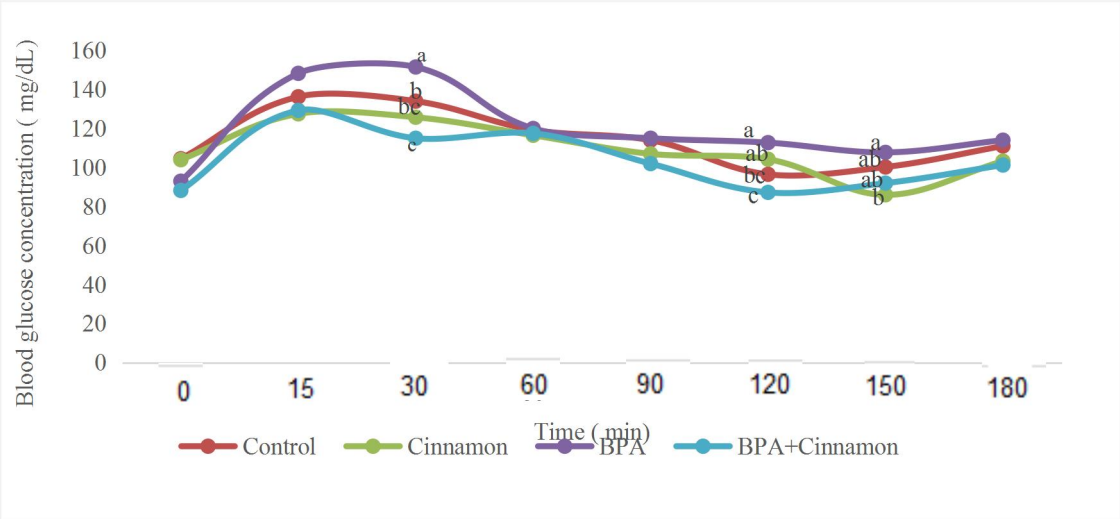

Fig 1: Oral Glucose Tolerance Test (OGTT) comparing glucose levels among rat groups control, CIN (400 mg/ kg), BPA (10 mg/ kg), and CIN (400 mg/ kg) + BPA (10 mg/ kg) in male Wistar rat.

3.3. Blood erythrocyte and differential leucocytic

Hematological examination results of the experimental groups were demonstrated in **(Table 2)**.
All the hematological parameters and leukocyte counts (total and differential) exhibited nonsignificant variation among groups.

Table 2: Effect of oral CIN administration on the haematological parameters and leukocyte counts (total and differential) of BPA -BPA-intoxicated male Wistar rats for three months

Values are represented as mean ± SE *(n=24)*.

	Control	CIN (400 mg/ kg)	BPA (10 mg/ kg)	BPA (10 mg/ kg) + CIN (400 mg/ kg)
Hemoglobin (g/L)	13.93 ± 0.66	13.80 ± 1.61	14.92 ± 0.34	15.00 ± 0.55
RBCs. Count (x10^{12} /L)	7.97± 0.39	7.33 ± 1.81	9.12 ± 0.10	8.18 ± 8.83
Hematocrit (L/L)	45.40± 2.13	38.62 ± 8.27	49.87 ± 0.98	40.54 ± 11.00
M.C.V (fL)	57.06 ± 1.16	57.40 ± 6.77	54.67 ± 0.76	56.22 ± 1.43
M.C.H (pg)	17.43 ± 0.38	23.62 ± 7.78	16.32 ± 0.30	16.87 ± 0.44
M.C.H.C (g/dL)	30.63 ± 0.08	38.97 ± 7.94	29.87 ± 0.17	30.05 ± 0.08
TLC	15.30 ± 2.83	14.20 ± 2.43	18.27 ± 1.54	12.92 ± 0.55
Neutrophils (x10^{9} /L)	45.00 ± 2.08	37.00 ± 1.91	36.75 ± 4.83	36.75 ± 5.43
Lymphocytes (x10^{9} /L)	43.00 ± 4.58	50.75 ± 2.78	49.25 ± 4.09	52.75 ± 4.62
Monocytes (x10^{9} /L)	11.00 ± 2.51	10.50 ± 1.65	12.75 ± 1.93	9.25 ± 1.37
Eosinophils (x10^{9} /L)	1.00 ± 0.00	1.75± 0.25	1.25 ± 0.25	1.25 ± 0.25
Basophiles (x10^{9} /L)	0.00	0.00	0.00	0.00
Platelets. Count (x10^{9} /L)	888.66 ± 42.46	906.75 ± 29.32	779.00 ± 112.25	842.25 ± 35.14

3.4. Biochemical parameters

Chronic similarly the levels of creatinine, urea, and uric acid as matched with the control group. The addition of CIN to the BPA group resulted in a statistical (P≤ 0.05) reduction in AST and ALT activities beside creatinine, urea, and uric acid values in serum as matched with the BPA rats. Moreover, the rats group treated with BPA exhibited statistical (P≤ 0.05) reduction in the total protein as matched with the control group. Meanwhile, the level of total protein in CIN + BPA rats statistically (P≤ 0.05) promoted as compared toxicity with BPA for three months induced a statistical (P≤ 0.05) increment in the ALT and AST activities with the BPA-intoxicated rats.

Moreover, the rats group treated with BPA demonstrated a statistical (P≤ 0.05) decline in albumin level as compared with the control group. There were statistically (P≤ 0.05) increased albumin levels in the rats group treated with CIN + BPA as matched with the BPA-treated rats **(Table 3)**.

Table 3: Effect of oral CIN administration on liver enzyme activities (AST, ALT), urea, creatinine, uric acid, total protein, and albumin of BPA-intoxicated male *Wistar* rats for three months

	Control	CIN (400 mg/ kg)	BPA (10 mg/ kg)	BPA (10 mg/ kg) + CIN (400 mg/ kg)
AST(U/L)	91.75± 0.14^{c}	88.50 ± 0.28^{d}	179.05 ± 0.91^{a}	155.75 ± 0.38^{b}
ALT(U/L)	24.15± 0.10^{c}	24.40 ± 0.08^{c}	54.00 ± 0.12^{a}	43.90 ± 0.32^{b}
Urea (mg/L)	15.21± 0.01^{c}	15.08 ± 0.01^{c}	40.42 ± 0.29^{a}	27.75 ± 0.15^{b}
Creatinine (mg/dL)	0.43 ± 0.00^{c}	0.43 ± 0.00^{c}	1.15 ± 0.01^{a}	0.82 ± 0.01^{b}
Uric acid (mg/)	2.23 ± 0.02^{c}	2.18 ± 0.01^{c}	4.62 ± 0.02^{a}	3.66 ± 0.01^{b}
Total protein (g/dL)	6.19 ± 0.01^{b}	6.24 ± 0.01^{a}	4.90 ± 0.01^{d}	5.09 ± 0.01^{c}
Albumin (g/dL)	4.21 ± 0.01^{a}	4.23 ± 0.01^{a}	3.48 ± 0.03^{c}	3.60 ± 0.00^{b}

Values are represented as mean ± SE *(n=24)*. Superscript letters (a, b, c, d) within the same row refer to significance at $P < 0.05$.

Administration of BPA for three months induced a statistical ($P \leq 0.05$) promotion in TG and TC levels while decreasing levels of HDL as compared with the control group. The CIN co-administration to the BPA group revealed a statistical ($P \leq 0.05$) reduction in TC and TG levels beside a statistical ($P \leq 0.05$) promotion in the HDL level as matched with the BPA-intoxicated rats **(Table 4)**.

3.5. Malondialdehyde (MDA) and total antioxidant capacity (TAC)

There was a statistical ($P \leq 0.05$) reduction in the level of TAC in the rat's group that received BPA as matched with the control ones. Meanwhile, the treatment of BPA-administered rats with CIN demonstrated a statistical ($P \leq 0.05$) promotion in TAC level as matched with the BPA group. Groups treated with BPA revealed a statistical ($P \leq 0.05$) promotion in the level of MDA as matched with the control one. The administrated group with CIN+ BPA exhibited a statistical ($P \leq 0.05$) lessening in MDA level as matched with the BPA rats **(Table 4)**.

3.6. HOMO-IR

There are non-statistical variations were noticed among groups in insulin resistance HOMO-IR **(Table 4)**.

3.7. Interluken-1beta (IL-1β), thyroid hormones (T3, T4) and insulin

Groups treated with BPA showed statistically ($P \leq 0.05$) promoted IL-1β levels as matched with the control rats. The administrated rat group with CIN + BPA exhibited a statistical ($P \leq 0.05$) reduction in IL-1β level as compared with the BPA group. BPA-intoxicated rats revealed a statistical ($P \leq 0.05$) reduction in T3 levels as matched with the control rats, giving CIN + BPA to rats induced statistically ($P \leq 0.05$) promoted T3 levels as compared with BPA-treated group. Intoxication with BPA induced no significant difference in T4 level as matched with the control rats. While a statistical ($P \leq 0.05$) promotion was noticed in T4 level when CIN co-administered with the BPA as matched with the BPA group. Oral gavage of BPA for three months exhibited non-significant variation in insulin**(Table 4).**

3.8. Leptin, resistin and adiponectin

The BPA-treated group showed significantly ($P \leq 0.05$) increased the levels of leptin and resistin as matched to the control rats. Administration of CIN + BPA to rats induced a statistical ($P \leq 0.05$) reduction in the levels of leptin and resistin as matched with the BPA intoxicated group. Moreover, rats given BPA demonstrated a statistical ($P \leq 0.05$) reduction in adiponectin level compared to the control rats. The levels of adiponectin statistically ($P \leq 0.05$) augmented in the co-administration BPA+ CIN group as matched with the BPA intoxicated group **(Table 4)**.

3.9. Histopathological analysis

The study revealed that there were no statistical variations between the CIN group and the control group **(Fig. 2A and 2B)**. However, in comparison to the control and CIN-supplemented rats, the liver from the BPA-treated group showed significant retrogressive changes in the parenchyma with signs of hemorrhage **(Fig. 2C).** In addition, congestion and distention of the central vein, discontinuity of endothelial lining, infiltration of inflammatory cells, widening of blood sinusoids and early signs of necrosis with fragmented nuclei of hepatocytes were evident **(Fig. 2D and 2E)**. Signs of micro and macro vacuolar degeneration (lipidosis) were also frequently apparent in studied hepatic sections **(Fig. 2F and 2G)**. However, BPA-treated sections co-administrated with CIN revealed marked improvement with low signs of hemorrhage between hepatocytes **(Fig. 2H)**. Likewise, no degenerative alterations were discovered in the kidneys of the groups that received CIN and control. The kidneys exhibited typical characteristics of Bowman's capsules, including intact epithelium in the glomerulus and renal tubules (both proximal and distal convoluted tubules). The results from the study of cortical sections revealed that revelation to BPA caused statistical pathological damage in the kidneys. This damage included glomerular atrophy, extension of acute proliferative glomerulonephritis, loss of glomerular epithelium, erosion of epithelial cells in the distal and proximal convoluted tubules, deformation of some tubules, and necrosis in others. In addition, cortical interstitial inflammation,

congested renal veins, renal interstitial edema, and hemorrhage were irregularly detected **(Fig. 3C)**. These perturbations were amended in the BPA + CIN group **(Fig. 3D)**.

Table 4: Effect of oral CIN administration on the biochemical parameters of BPA-intoxicated male Wistar for three months

	Control	CIN (400 mg/ kg)	BPA (10 mg/ kg)	BPA (10 mg/ kg) + CIN (400 mg/ kg)
IL-1β (pg/mL)	3.93 ± 0.01^{c}	3.87 ± 0.02^{c}	14.69 ± 0.01^{a}	8.74 ± 0.03^{b}
TAC (mM/L)	1.68 ± 0.01^{b}	1.75 ± 0.01^{a}	0.88 ± 0.00^{d}	1.12 ± 0.00^{c}
MDA (nmol/mg)	1.71 ± 0.00^{c}	1.70 ± 0.00^{d}	3.79 ± 0.00^{a}	3.00 ± 0.00^{b}
TC (mg/dL)	54.88 ± 0.20^{c}	54.32 ± 0.39^{c}	120.36 ± 0.74^{a}	69.74 ± 0.70^{b}
TG (mg/dL)	62.45 ± 0.22^{d}	65.11 ± 0.39^{c}	144.80 ± 0.57^{a}	83.88 ± 0.31^{b}
HDL (mg/dL)	19.57 ± 0.09^{b}	24.46 ± 0.15^{a}	13.97 ± 0.21^{c}	15.68 ± 0.14^{d}
T3 (ng/dL)	2.56 ± 0.00^{a}	2.55 ± 0.00^{a}	1.57 ± 0.00^{c}	1.91 ± 0.02^{b}
T4 (µg/dL)	4.17 ± 0.00^{ab}	4.16 ± 0.00^{c}	4.16 ± 0.00^{bc}	4.17 ± 0.00^{a}
Insulin (µU/mL)	1.23 ± 0.00	1.23 ± 0.00	1.24 ± 0.00	1.23 ± 0.00
Leptin (ng/mL)	274.70 ± 1.53^{c}	277.61 ± 1.41^{c}	512.21 ± 2.75^{a}	464.30 ± 4.40^{b}
Resistin (ng/mL)	3.32 ± 0.03^{c}	3.36 ± 0.01^{c}	8.70 ± 0.00^{a}	7.09 ± 0.01^{b}
Adiponectin (µg/mL)	8.87 ± 0.00^{a}	8.86 ± 0.01^{a}	4.78 ± 0.03^{c}	6.84 ± 0.02^{b}
HOMO-IR	0.31 ± 0.01	0.32 ± 0.00	0.28 ± 0.00	0.26 ± 0.02

Values are represented as mean ± SE (n=24). Superscript letters (a, b, c, d) within the same row refer to significance at $P < 0.05$.

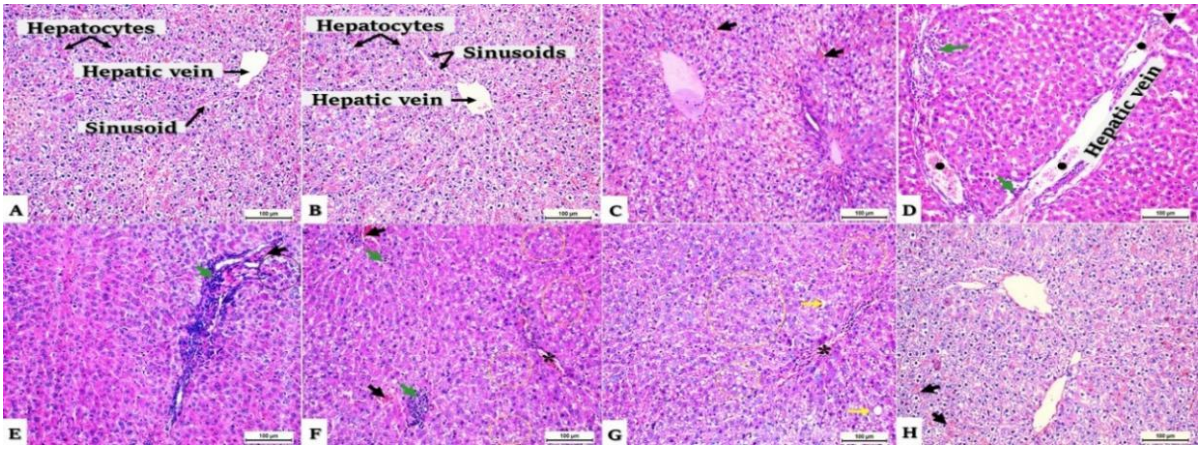

Fig. 2 (A-H): Representative microphotographs of hepatic tissues in male Albino rats. (A) control and (B) CIN (400 mg/ kg) groups showing normal hepatocytes and hepatic blood vessels (veins and sinusoids). (C-G) The BPA-intoxicated group (10 mg/ kg) showed marked destruction of hepatic architecture, hemorrhage (black arrows), enlargement and congestion of the central vein (•) with discontinuity of endothelium lining (▼), inflammation (green arrows), widening and congestion of blood sinusoids (*), signs of hepatocellular necrosis (black circles) with fragmented nuclei, and multiple vacuolar degenerations; micro (yellow circles) and macro (yellow arrows). (H) The BPA (10 mg/ kg) + CIN (400 mg/ kg) group showed typical liver architecture with a minor degree of haemorrhage. Haematoxylin and eosin stain, Mag. X 200, Bars = 100 µm.

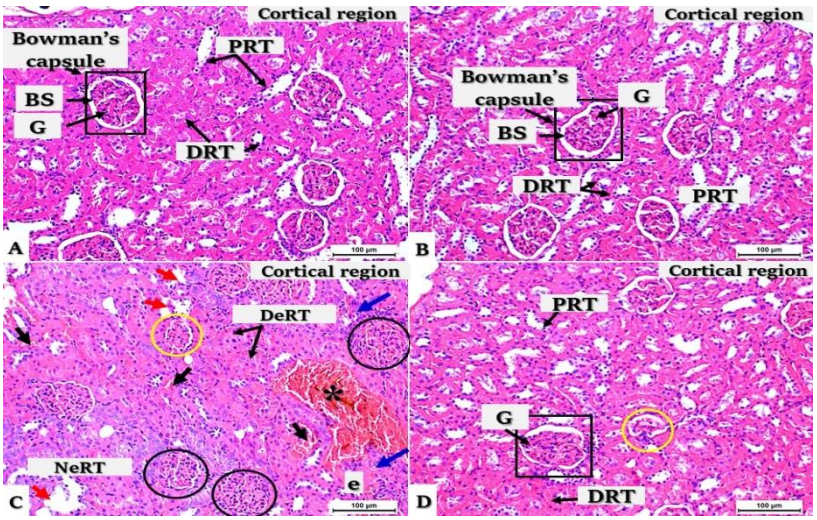

Fig. 3 (A-D): Representative microphotographs of cortical region of renal tissues in male *Albino* rats. (A) control and (B) CIN (400 mg/ kg) groups showed normal Bowman's capsules, intact epithelium in the glomerulus (G), Bowman's space (BS), normal proximal (PRT) and distal convoluted tubules (DRT). (C) The BPA (10 mg/ kg) -treated group showed glomerular atrophy (yellow circle), acute proliferative glomerulonephritis (black circles), epithelial erosion in the convoluted tubules (red arrows), tubular deformation (DeRT), renal tubular necrosis (NeRT), cortical interstitial inflammation (blue arrow), congested renal vein (*), edema (e), and hemorrhage (black arrows). (D) The BPA (10 mg/ kg) + CIN (400 mg/ kg) group showed mildly inflamed glomerulus (G), few appearing atrophy (yellow circle), and the major restoration of the glomerular epithelium (square), with normal PCT and DCT. Hematoxylin and eosin stain, Mag. X 200, Bars = 100 µm.

4. Discussion

Recently, lots of metabolic disorders have been increased, and several studies investigated the actual causes, but there is no sure result showing the cause; various animal studies suggested that endocrine disruptors are the first possible reason for BPA. Acquaintance to BPA primes the presence of disturbances in metabolism like obesity, alteration of glucose homeostasis, and retrograde influences on biochemical parameters [37]. Actually, BPA increases the oxidative load in the body by upsetting the antioxidant/prooxidant homeostasis inside the cells [38]. So, this study investigated the mitigation influence of the CIN aqueous extract versus the metabolic adverse influences of BPA.

This study, throughout 90 continuous days, showed non-statistical alteration in body weight gain and the final body weight among the tested groups. These outcomes were same as the later reports of Takahashi and Oishi [39], Bindhumol, et al. [40], and Morgan, et al. [38]. On the other side, contradictory results were shown by Razzoli, et al. [41]. They declared that 0.1 mg/kg BPA induced a statistical decrease in body weight as matched with the control ones. Aboul Ezz, et al. [42] declared a considerable rise in the of gain body weight of BPA-treated animals. These discrepancies may be claimed to the treatment period, dose, routes, food type, sex, or strains of rats.

Based on the present study results, absolute epididymal fat mass, absolute sublumbar fat mass, relative epididymal and sublumbar fat masses were increased in the BPA group as matched to the control ones. These outcomes were consistent with the previous report of Hoque, et al. [43]. BPA, this estrogenic compound, could inhibit adiponectin secretion via its binding to estradiol receptors, specifically ERα and ERβ, also BPA could reduce adiponectin production while increasing inflammatory cytokines via working on macrophages and adipocytes [44]. Oxidative stress and mitochondrial malfunction lead to increased adipocyte differentiation and fat accumulation, in addition to insulin resistance [45]. The existence of cytokines for inflammation, like IL-6, induces inflammatory response in the fat tissue, inhibits lipolysis, and hence increases the fat masses[46].

The contemporary study declared that the gavage of CIN to the BPA group induced a statistical reduction in absolute epididymal fat mass, absolute sublumbar fat mass, relative epididymal and sublumbar fat masses as matched to the BPA-administered group. CIN aqueous extract pretreatment may reduce body weight by decreasing fat mass percentage, consistent with Kabuto, et al. [47]. So, the treatment with CIN aqueous extract mitigated the negative effects of BPA by acting as an antioxidant on these tissues, adipocytes may produce or secrete less adiponectin, leading to the progress of insulin-resisting adipokines [48], CIN extract possesses antioxidative properties owing to the capability of phenolic components to sequestrate ROS. Cinnamic acid and coumarin can scavenge hydroxyl radicals, superoxide anions, and other free radicals [49]. CIN has been shown to improve glycogen storage by modulating glycogen synthesis activity [50]. CIN extract has a potential role as a blood glucose reducing agent; this could be due to the existence of antioxidant chemicals like Type-A Polymer water-soluble polyphenol, which affects and lowers the resistance of insulin. Moreover, the presence of cinnamic acid, and cinnamaldehyde in the CIN aqueous extract [51-53]. Actually, CIN extract enhances glucose transfer or acceptance by glucose transporters, specifically GLU-4, in brown fat tissue and muscles [54].

The study results of OGTT demonstrated a significantly elevated glucose level in the rat groups administrated with BPA as matched with the control rats. CIN administration to BPA-intoxicated group significantly mitigated the increased blood glucose values as matched with the BPA group. These results have coincided with later research of Alonso-Magdalena, et al.[55] & Nadal, et al. [56]. BPA may cause glucose intolerance and disrupt β cell function of pancreas [57]. Pancreatic injury causes decreased insulin release and elevated blood glucose levels [58]. CIN possesses insulin-like properties, comprising the ability of biologically active ingredients to trigger receptors of insulin kinase, increase glucose absorption, autophosphorylation of the receptors of insulin, and the activity of glycogen synthase [59]. CIN extract improved insulin sensitivity and increased glucose intake [60]. Ingredients of CIN that are water soluble have been discovered to boost the efficacy of signaling the insulin system and, hence, diminish glucose levels [61]. CIN extract promotes uptake of the glucose via instigation of the activity of insulin receptor kinase, promoting synthesis of the glycogen, suppressing gluconeogenesis by influencing the principal regulatory enzymes, enhancing the release of insulin, and stimulating the function insulin receptors[62]. Moreover, CIN aqueous extract can improve the uptake of glucose and the synthesis of glycogen via stimulating synthesis of glycogen while hindering glycogen synthase kinase 3B and falling the intestinal glucose absorption by boosting the activity of glycosidase enzyme. Furthermore, the CIN extract significantly abridged alanine in the digestive system of rat, which constitutes an important part of hepatic gluconeogenesis [63].

In the existing study, all the hematological parameters and leukocyte counts (total and differential) exhibited nonsignificant variation among the experimental groups. These results match with the former outcomes of Ahmed, et al. [64]. Many other studies with high BPA doses revealed statistical decline in hematological parameters [65-69].

Activities of hepatic ALT and AST in the BPA-administered group were significantly increased as matched with the control. These results harmonized with Hassan, et al. [25], and Mahmoudi, et al. [70]. ALT and AST are essential enzymes linked with hepatic parenchymal cells, when there is liver damage, these enzymes seep into the bloodstream and are evaluated, As liver damage progresses, both enzymes become more active [71]. The ALT and AST activities were statistically increased; these were attributed to the impairment in the hepatic tissue [72, 73]. These elevations in the liver enzymes activity may be claimed to overrun of reactive oxygen species ROS may harm the integrity of hepatocytes structure, resulting in a rise in liver serum indicators [74]. The study showed the administration of CIN with BPA promoted a statistical decline in AST and ALT activities as matched with the BPA ones. This finding is consistent with Torabi, et al. [75]. The decrease in the levels of enzymes (ALT and AST) beside the hepatoprotective effect of the CIN aqueous extract was attributed to its antioxidative properties, which can quench ROS and rouse general antioxidant system of cells [76].

Total protein and albumin results showed a statistical decline in the BPA-intoxicated rat group as matched with the control rat group. These results were harmonized with Geetharathan and Josthna [77] and Moon, et al. [78]. Albumin constitutes about half the protein content in serum; a diminution in albumin is usually allied to a reduction in total protein, even if most other proteins are exist in normal concentrations; a decline in total protein in serum may reflect augmented protein loss or reduced protein synthesis [79]. Serum total protein content is thought to reflect a symmetry between the rates of protein creation and decline. Moreover, BPA is established to produce mitochondrial oxidative stress which leads to protein damage[80, 81]. The CIN-pretreated rat group, which was intoxicated by BPA, showed significantly elevated levels of albumin and total protein in the serum as matched with the BPA-intoxicated rat group. These results obtained were concurring with those presented by Elshopakey and Elazab [82]. CIN extract showed elevated serum total protein levels to approximately normal levels, indicating hepatoprotective action; CIN extract and its active component, cinnamaldehyde, have been shown to effectively restore liver enzymes to acceptable levels by stimulating protein synthesis, which promotes liver cell creation and regeneration [83].

Chronic toxicity with BPA for three months encouraged a statistical increment in the serum urea, creatinine, and uric acid levels as compared to the control one, these parameters are mostly used in the assessment of kidney functions; these results were consistent with findings that were reported by Bancroft and Gamble [36]. The study reflects that BPA has an undesirable influence on the renal tissue and principals adverse impacts on kidney function, the diminished capability to waste products excretion like (urea, creatinine, and uric acid) can be resulted in a defect tubular function and glomerular filtration as detected in the current histological renal sections. The impairments in renal function noticed reflect the destructive effect of BPA on the renal glomeruli [84]. Creatinine is often used to indicate glomerular function [85]. Kidney injury impairs the kidney's ability to eliminate creatinine and urea, resulting in their accretion in the blood; as a result, raised blood creatinine and urea levels, usually, creatinine high levels in the blood, are castoff as a pointer of kidney damage [86].

Previous research has reported that oxidative stress is known as an inequity in the generation of ROS and antioxidant defenses that causes oxidative damage; exposure to BPA diminishes the antioxidants; superoxide dismutase enzyme (SOD) and glutathione (GSH) in renal tissues, this disproportion generated kidney oxidative stress leading to oxidative damage in kidney with increased MDA as an index for lipid peroxidation.

The standard range of creatinine levels in rats' sera are 0.2–0.8 mg/dl [87]. The herein study demonstrated that the creatinine level in BPA-intoxicated rats was 1.15 mg/dl while the BPA-treated rat that co-administrated with CIN extract showed a significant reduction in creatinine level almost considered as maximum normal range of 0.82 mg/dl. CIN has mitigated the adverse outcome of BPA on kidneys' parameters. This was harmonized with the previous conclusion of Lusiana, et al. [88]. Moreover, previous studies recorded that cinnamaldehyde considered as the main active constituent of CIN extract components has been demonstrated to hinder the levels of urea and creatinine and has a highly effective antioxidant role in the kidney tissues, the machinery that takes part by overwhelming oxidative stress from several oxidative reactions that happen in the kidneys, as well as flavonoids, Alkaloids, cinnamaldehyde, tannins, saponins, and polyphenols, are chemical compounds found in CIN extract that can hinder the existence of lipid peroxides by stopping free radicals and promoting the antioxidants concentration inside cells also have anti-inflammation assets [89, 90].

Intoxication of BPA for 3 months induced a statistical increment in TC and TG levels while decreasing HDL levels than control. These outcomes were harmonized with that obtained by Marmugi, et al. [91] and Robertson, et al. [92]. This

research proposes that BPA oral exposure may cause and accelerate hyperlipidemia by disturbing oxidative systems which leads to damage or dysfunction in the hepatocytes and mitochondrion in adult male rats. The higher TC and TG levels obtained here may be the outcome of the noticed BPA-provoked peroxidative influences, which were inveterate via the hepatic histological changes. Previous research suggests that free BPA causes free radicals and oxidative stress generation[93]. Antioxidants, both enzymatic and non-enzymatic, constitute a crucial role in counteracting the influences of ROS. The dramatic decrement in catalase activity in BPA-exposed livers designates a disturbed oxidant-antioxidant equilibrium, which leads to membrane damage, while decreased catalase activity has been linked with a statistical increase in ROS production [94, 95]. The herein study demonstrated that the co-administration of CIN + BPA caused a statistical reduction in TG and TC levels beside a statistical promotion in the HDL level as matched with the BPA rats. These outcomes were parallel to those presented by Khan, et al. [96] and Alsoodeeri, et al. [97]. CIN extract, in addition to its antioxidant properties, may reduce hyperlipidemia by constraining β-hydroxy β-methylglutaryl-CoA reductase, a lipid metabolism enzyme; this action reduces cholesterol synthesis in the hepatic cells and suppresses the peroxidation of lipids [98]. Promoted lecithin cholesterol acyl transferase activity by CIN, which regulates blood lipids, can lead to higher HDL levels [99, 100]. Cinnamon's lipolytic effect may induce lower TG levels hence inhibiting TG synthesis that may contribute to the low blood TG level [101].

Previous research has reported that oxidative stress is known as an inequity in the generation of ROS and antioxidant defenses that causes oxidative damage; exposure to BPA diminishes the antioxidants; superoxide dismutase enzyme (SOD) and glutathione (GSH) in renal tissues, this disproportion generated kidney oxidative stress leading to oxidative damage in kidney with increased MDA as an index for lipid peroxidation.

The standard range of creatinine level in rats' sera is 0.2–0.8 mg/dl [87]. The herein study demonstrated that the creatinine level in BPA intoxicated rats was 1.15 mg/dl while the BPA-treated rat that co-administrated with CIN extract showed a significant reduction in creatinine level almost considered as maximum normal range 0.82 mg/dl. CIN has mitigated the adverse outcome of BPA on kidneys' parameters. This was harmonized with the previous conclusion of Lusiana, et al.[88]. Moreover, previous studies recorded that cinnamaldehyde considered as a main active constituent of CIN extract components has been demonstrated to hinder the levels of urea and creatinine and has a highly effective antioxidant role in the kidney tissues, the machinery that takes part by overwhelming oxidative stress from several oxidative reactions that happen in the kidneys, as well as flavonoids, Alkaloids, cinnamaldehyde, tannins, saponins, and polyphenols, are chemical compounds found in CIN extract that can hinder the existence of lipid peroxides by stopping free radicals and promoting the antioxidants concentration inside cells also have anti-inflammation assets [89, 90].

Intoxication of BPA for 3 months induced a statistical increment in TC and TG levels while decreasing HDL levels than control. These outcomes were harmonized with that obtained by Marmugi, et al. [91] and Robertson, et al. [92]. This research proposes that BPA oral exposure may cause and accelerate hyperlipidemia by disturbing oxidative systems which lead to damage or dysfunction in the hepatic cells and mitochondrion in adult male rats. The higher TC and TG levels obtained here may be the outcome of the noticed BPA-provoked peroxidative influences, which were inveterate via the hepatic histological changes. Previous research suggests that free BPA causes free radicals and oxidative stress generation[93]. Antioxidants, both enzymatic and non-enzymatic, constitute a crucial role in counteracting the influences of ROS. The dramatic decrement in catalase activity in BPA-exposed livers designates a disturbed oxidant-antioxidant equilibrium, which leads to membrane damage, while decreased catalase activity has been linked with a statistical increase in ROS production [94, 95]. The herein study demonstrated that the co-administration of CIN + BPA caused a statistical reduction in TG and TC levels beside a statistical promotion in the HDL level as matched with the BPA rats. These outcomes were parallel to those presented by Khan, et al. [96] and Alsoodeeri, et al. [97]. CIN extract, in addition to its antioxidant properties, may reduce hyperlipidemia by constraining β-hydroxy β-methylglutaryl-CoA reductase, a lipid metabolism enzyme; this action reduces cholesterol synthesis in the hepatic cells and suppresses the peroxidation of lipids [98]. Promoted lecithin cholesterol acyl transferase activity by CIN, which regulates blood lipids, can lead to higher HDL levels [99, 100]. Cinnamon's lipolytic effect may induce lower TG levels hence inhibiting TG synthesis that may contribute to the low blood TG level [101]. There was a statistical upsurge in MDA and IL-1β levels in rat groups that received BPA as matched with the control ones, while the TAC was declined. The results presented in this study were harmonized with previous reports by Elswefy, et al. [102]. Moreover, Abdelrazek, et al. [103] noticed that the BPA treatment caused immunological change, including increased IL-1β levels, which were attributed to ROS and BPA's ability to trigger lipid peroxidation. Rats treated with BPA had significantly increased MDA levels, which suggest that the antioxidant-oxidant balance was disturbed; oxidative stress disrupts the equilibrium between the antioxidant and oxidant systems in cells. Causing damage to the antioxidant system by BPA toxicity can be designated as oxidative damage and the production of free radicals, as well as the deterioration of cell integrity in mammals; lipid peroxidation products such as MDA frequently induce neurotoxicity, hepatotoxicity, and nephrotoxicity; this appears throughout increasing the MDA levels and decreasing the TAC in rats' organs and tissues [104, 105]. The rat group administered with CIN + BPA exhibited a statistical decline in IL-1β and MDA levels as matched with the BPA group, with a statistical promotion of the TAC level. The later results were coincided with the study Das, et al. [106]. Theorizing that after administration of CIN extract, there is lesser vulnerability to cellular oxidative damage, may be owing to the existence of flavonoids [107]. Extracted polyphenol type-A procyanidin from CIN bark shows anti-inflammatory potentials in rats [108].

The BPA rats treated group revealed a statistical increase in leptin and resistin levels as matched to the control ones, while the adiponectin level was significantly reduced. Also, in the current research, there are non-statistical variations among groups, neither insulin levels nor insulin resistance HOMO-IR. These findings were in harmonization with that of Elgawish, et al. [109], Ariemma, et al. [110] and Ahangarpour, et al. [111]. Resistin and leptin, among these hormones, constitute potential interplays in glucose homeostasis and body weight regulation, resistin and leptin act in opposite ways with similar outcomes. They intermingle with each other, usually rising levels of resistin and leptin appear in obesity models of rodents. Such obesity can happen either by fat nutrition or chronic exposure of living organisms for contaminations like BPA. This phenomenon is closely associated with adipocytes-secreted signaling molecules such as adiponectin, fatty acids, leptin, and

resistin, resulting in glucose imbalance and hence led to obesity [112]. BPA alters the normal endocrine paths in adipose tissue, leading to an amplified hazard of obesity [113]. Adipocytes produce resistin and leptin, which are cytokines [114]. Chronic inflammation is a consequence ad for these adipokines secretion [115]. This may lead to many degenerative disorders[114]. Leptin and resistin lead to promoted ROS [116, 117]. Furthermore, they lead to an increment in cytokines of inflammation [118, 119]. The increased leptin and resistin encounters for the increased glucose level observed during OGGT observed in the current study. Several studies illustrated that the close association between the resistance of insulin and high resistin plasma levels in obese cases [120]. BPA, an estrogenic chemical, can inhibit adiponectin secretion by dimerization to estradiol receptors, specifically ERβ and ERα, BPA affects macrophages and adipocytes, decreasing adiponectin and increasing cytokines of inflammation [44]. Administration of CIN with BPA to rats persuaded a statistical decline in leptin and resistin levels as matched with the BPA group while increasing adiponectin concentration. These outcomes were in harmony with that of Sfar, et al. [121] and Friedman [122]. CIN is known for its ability to mimic insulin [123, 124]. CIN extract can increase autophosphorylation of insulin receptors and inhibit protein tyrosine phosphatase-1, which disables the insulin receptor in fat cells; CIN may impact protein phosphorylation and dephosphorylation in intact adipocytes [61]. CIN extract prevents insulin resistance in rats, this is due to the stimulation of insulin signaling, potentially through the NO route in skeletal muscle. These effects could be encountered in the normalized plasma lipid profile in the BPA + CIN group. CIN extract enhances the function of insulin receptors by inhibiting phosphatase and activation of kinase, while hindering the enzyme that averts insulin receptor connection. This condition triggers the phosphorylation of insulin receptors, which enhances its actions [124]. CIN promotes glucose absorption and glycogen production by triggering glycogen synthase and inhibiting glycogen synthase Kinase 3β, limiting intestinal glucose absorption [63, 125, 126]. Cinnamate, an ingredient found in CIN bark, drops cholesterol levels by hindering liver 5-hydroxy-3- methylglutaryl-CoA reductase activity in rats [98]. So, this suggested mechanism, as well as the antioxidant abilities of flavonoid components, may interpret the decreased levels of leptin and resistin of CIN-treated rats due to diminished fat mass of adipose tissue and, of course, decrease the mentioned hormones when adipose tissues return to its normal size and mass. Adiponectin hormone affects various biological activities in the adipose tissue. Serum concentrations of this adipokine decrease with chronic illnesses and resistance to insulin [127].

Rats that were given BPA produced a statistical lessening in T3 and T4 levels. These results were harmonized with Moriyama, et al. [128]. The BPA administration influences the thyroid system by inhibiting thyroperoxidase enzyme activity and/or weakly binds to the T3 and T4 receptors (Schmutzler et al., 2007; Moriyama et al., 2002; BPA acts as an antagonist to T3, which inhibits transcription activity of these receptors' activation [129]. Furthermore, decreased TAC in the BPA group led to oxidative load and elevated ROS, resulting in fragmentation of DNA and degenerative changes in the thyroid tissue[130]. Moreover, there were significant increases in T3 and T4 levels with the co-administration of CIN with the BPA rats group matched to the BPA rats. These outcomes were in agreement with Gaique, et al. [131]. These findings refer to the ability of CIN aqueous extract to amend the adversative potentials of endocrine disruptors on the levels of thyroid hormone, which could be claimed to the existence of several bio-active ingredients in the CIN extract [132, 133].

The histopathological results showed significant hepatic tissue disturbances, including lipidosis and inflammation with signs of hepatocellular necrosis. These findings align with those of the Amin, et al. [134] study, which demonstrated that giving adult male albino rats 50 mg/kg of BPA orally for 2 months leads to liver injury and oxidative stress. Moreover, the herein results deep-rooted the outcomes of earlier studies declaring that BPA administration male offspring mice induced lipid accumulation and fatty liver through the upregulation of PPARγ and inhibition of HNF1b [135]. Additionally, BPA exposure can result in extreme de novo fatty acid synthesis, leading to lipid gathering in the hepatocytes and afterward increasing serum lipid profile [134]. The liver function tests, including AST, ALT, total protein, TG, and TC, were used to judge the occurrence of hepatic inflammation or injury.

Cinnamon co-treatment (400 mg/kg) with BPA improved the liver appearance, thus reflected on the restored liver profile, including AST, ALT, total protein, TG, and TC biomarkers. Previous studies have been found that CIN has a protective effect due to its phytoconstituents such as flavonoids and phenolic contents, which help in free radicals scavenging and reducing oxidative stress, the chief machinery of action [136].

The severe kidney lesions noticed in the BPA-intoxicated rats align with earlier reports of Ola-Davies and Olukole[137] and Nuñez, et al. [138]. These findings reflect that BPA hurts the kidneys and leads to a worsening of kidney function, as it correlates positively with currently obtained data on the elevated urea, creatinine, and uric acid levels in our study. It is settled that the alteration of renal tubular function after BPA administration results from both BPA-induced glomerular and tubular dysfunctions [135]. The study found that co-administration of CIN to the BPA-contaminated rats prevented BPA-induced nephrotoxicity. The improvements in creatinine, urea, and uric acid within the retrogressive deviations in renal structure all supported this conclusion. In the same line, parallel results were gained by Morgan, et al.[139] study, which concluded that CIN could amend the renal toxic oxidative influences of BPA, representing its shielding antioxidant potential.

5. Conclusions

Chronic oral exposure to BPA causes metabolic dysfunction in adipocytes, hypothyroidism, and glucose intolerance. The negative effects were linked to decreased antioxidant reserves and increased adipokines and inflammatory cytokines. Co-administration of CIN aqueous extract with BPA enhanced glucose homeostasis, fat mass, and thyroid hormones, perhaps alleviating inflammation and oxidative stress in BPA-provoked metabolic disturbances. CIN components have antioxidant properties that prevent BPA-induced metabolic syndrome or diminish the negative adverse effect of BPA to the almost normal range.

6. Abbreviations

B. wt.: body weight; TLC: Total Leucocyte Cont.: M.C.H.C: Mean corpuscular haemoglobin concentration; M.C.H: Mean corpuscular haemoglobin; M.C.V: mean corpuscular volume; PC: Poly Carbonate; ED: Endocrine Disruptors; BPA: Bisphenol A; CIN: Cinnamon; T3: Triiodothyronine; T4: Thyroxine; HDL: High-density lipoprotein; TG: Tri-glyceride; TC: Total Cholesterol; RBCs: Red blood cells; MDA: Malondialdehyde; IL-1β: Interleukin-1 beta; TAC: Total Antioxidant Capacity; ALT: Alanine aminotransferase; AST: Astatine aminotransferase; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; OGTT: Oral Glucose Tolerance Test;

7. Conflict of interest

The authors declare no conflict of interest for the publication of this paper.

8. Funding

For this research, the authors did not receive any special funding from public, private, or nonprofit organizations.

9. References

[1] M.-K. Yeo and M. Kang, "Photodecomposition of bisphenol A on nanometer-sized TiO2 thin film and the associated biological toxicity to zebrafish (Danio rerio) during and after photocatalysis," *Water research,* vol. 40, no. 9, pp. 1906-1914, 2006.

[2] C. Han and Y.-C. Hong, "Bisphenol A, hypertension, and cardiovascular diseases: epidemiological, laboratory, and clinical trial evidence," *Current hypertension reports,* vol. 18, no. 2, pp. 1-5, 2016.

[3] B. Bae, J. Jeong, and S. Lee, "The quantification and characterization of endocrine disruptor bisphenol-A leaching from epoxy resin," *Water Science and Technology,* vol. 46, no. 11-12, pp. 381-387, 2002.

[4] J. Biles, T. McNeal, T. Begley, and H. Hollifield, "Determination of bisphenol-A in reusable polycarbonate food-contact plastics and migration to food-simulating liquids," *Journal of agricultural and food chemistry,* vol. 45, no. 9, pp. 3541-3544, 1997.

[5] Y. Sun, M. Wada, O. Al-Dirbashi, N. Kuroda, H. Nakazawa, and K. Nakashima, "High-performance liquid chromatography with peroxyoxalate chemiluminescence detection of bisphenol A migrated from polycarbonate baby bottles using 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoyl chloride as a label," *Journal of Chromatography B: Biomedical Sciences and Applications,* vol. 749, no. 1, pp. 49-56, 2000.

[6] D. Melzer, N. E. Rice, C. Lewis, W. E. Henley, and T. S. Galloway, "Association of urinary bisphenol a concentration with heart disease: evidence from NHANES 2003/06," *PloS one,* vol. 5, no. 1, p. e8673, 2010.

[7] K. Chitra, C. Latchoumycandane, and P. Mathur, "Effect of nonylphenol on the antioxidant system in epididymal sperm of rats," *Archives of toxicology,* vol. 76, pp. 545-551, 2002.

[8] A. H. Kamel, M. A. Foaud, and H. M. Moussa, "The adverse effects of bisphenol A on male albino rats," *The Journal of Basic and Applied Zoology,* vol. 79, no. 1, pp. 1-9, 2018.

[9] L. Tapsell, "Health benefits of herbs and spices: the past, the present, the future," *Med J Aust,* vol. 185, pp. S4-S24, 2006.

[10] S. Sen, R. Chakraborty, and B. De, "Challenges and opportunities in the advancement of herbal medicine: India's position and role in a global context," *Journal of Herbal medicine,* vol. 1, no. 3-4, pp. 67-75, 2011.

[11] A. Sharma, C. Shanker, L. K. Tyagi, M. Singh, and C. V. Rao, "Herbal medicine for market potential in India: an overview," *Acad J Plant Sci,* vol. 1, no. 2, pp. 26-36, 2008.

[12] C. Ulbricht *et al.*, "An evidence-based systematic review of cinnamon (Cinnamomum spp.) by the Natural Standard Research Collaboration," *Journal of dietary supplements,* vol. 8, no. 4, pp. 378-454, 2011.

[13] X. Sheng, Y. Zhang, Z. Gong, C. Huang, and Y. Zang, "Improved Insulin Resistance and Lipid Metabolism by Cinnamon Extract through Activation of Peroxisome Proliferator-Activated Receptors," *PPAR Research,* vol. 2008, pp. 581348-581348, 2008.

[14] S. Kumar, N. Vasudeva, and S. Sharma, "GC-MS analysis and screening of antidiabetic, antioxidant and hypolipidemic potential of Cinnamomum tamala oil in streptozotocin induced diabetes mellitus in rats," *Cardiovascular Diabetology,* vol. 11, p. 95, 2012.

[15] L. K. Chao, K.-F. Hua, H.-Y. Hsu, S.-S. Cheng, J.-Y. Liu, and S.-T. Chang, "Study on the antiinflammatory activity of essential oil from leaves of Cinnamomum osmophloeum," *Journal of Agricultural and Food Chemistry,* vol. 53, no. 18, pp. 7274-7278, 2005.

[16] P. Crawford, "Effectiveness of cinnamon for lowering hemoglobin A1C in patients with type 2 diabetes: a randomized, controlled trial," *The Journal of the American Board of Family Medicine,* vol. 22, no. 5, pp. 507-512, 2009.

[17] N. Matan, H. Rimkeeree, A. Mawson, P. Chompreeda, V. Haruthaithanasan, and M. Parker, "Antimicrobial activity of cinnamon and clove oils under modified atmosphere conditions," *International journal of food microbiology,* vol. 107, no. 2, pp. 180-185, 2006.
[18] B. Shan, Y.-Z. Cai, J. D. Brooks, and H. Corke, "The in vitro antibacterial activity of dietary spice and medicinal herb extracts," *International Journal of food microbiology,* vol. 117, no. 1, pp. 112-119, 2007.
[19] S. Koppikar, A. Choudhari, S. Suryavanshi, S. Kumari, S. Chattopadhyay, and R. Kaul-Ghanekar, "Aqueous cinnamon extract (ACE-c) from the bark of Cinnamomum cassia causes apoptosis in human cervical cancer cell line (SiHa) through loss of mitochondrial membrane potential," *BMC Cancer,* vol. 10, pp. 210-210, 2010.
[20] J. Lu, K. Zhang, S. Nam, R. Anderson, R. Jove, and W. Wen, "Novel angiogenesis inhibitory activity in cinnamon extract blocks VEGFR2 kinase and downstream signaling," *Carcinogenesis,* vol. 31, no. 3, pp. 481-488, 2009.
[21] R. A. Anderson *et al.*, "Cinnamon extract lowers glucose, insulin and cholesterol in people with elevated serum glucose," *Journal of traditional and complementary medicine,* vol. 6, no. 4, pp. 332-336, 2016.
[22] S. M. Blevins, M. J. Leyva, J. Brown, J. Wright, R. H. Scofield, and C. E. Aston, "Effect of cinnamon on glucose and lipid levels in Non–insulin-dependent type 2 diabetes," *Diabetes care,* vol. 30, no. 9, pp. 2236-2237, 2007.
[23] M. Ciftci, U. G. Simsek, A. Yuce, O. Yilmaz, and B. Dalkilic, "Effects of dietary antibiotic and cinnamon oil supplementation on antioxidant enzyme activities, cholesterol levels and fatty acid compositions of serum and meat in broiler chickens," *Acta Veterinaria Brno,* vol. 79, no. 1, pp. 33-40, 2010.
[24] M. Shalaby and A. Hamowieh, "Safety and efficacy of Zingiber officinale roots on fertility of male diabetic rats," *Food and chemical toxicology,* vol. 48, no. 10, pp. 2920-2924, 2010.
[25] Z. K. Hassan *et al.*, "Bisphenol A induces hepatotoxicity through oxidative stress in rat model," *Oxidative medicine and cellular longevity,* vol. 2012, 2012.
[26] R. A. Pederson, H. A. White, D. Schlenzig, R. P. Pauly, C. H. McIntosh, and H.-U. Demuth, "Improved glucose tolerance in Zucker fatty rats by oral administration of the dipeptidyl peptidase IV inhibitor isoleucine thiazolidide," *Diabetes,* vol. 47, no. 8, pp. 1253-1258, 1998.
[27] R. Hoffman, E. J. Benz Jr, L. E. Silberstein, H. Heslop, J. Anastasi, and J. Weitz, *Hematology: basic principles and practice*. Elsevier Health Sciences, 2013.
[28] G. Toro and P. G. Ackermann, "Practical clinical chemistry," *(No Title),* 1975.
[29] J. R. Duncan, E. A. Mahaffey, and K. W. Prasse, *Veterinary laboratory medicine*. Iowa State University Press Ames, 1994.
[30] I. Greenwald, "The chemistry of Jaffe's reaction for creatinine II. The effect of substitution in the creatinine molecule and a possible formula for the red tautomer1," *Journal of the American Chemical Society,* vol. 47, no. 5, pp. 1443-1448, 1925.
[31] C. C. Allain, L. S. Poon, C. S. Chan, W. Richmond, and P. C. Fu, "Enzymatic determination of total serum cholesterol," *Clinical chemistry,* vol. 20, no. 4, pp. 470-475, 1974.
[32] P. Fossati and L. Prencipe, "Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide," *Clinical chemistry,* vol. 28, no. 10, pp. 2077-2080, 1982.
[33] N. Rifai, G. R. Warnick, and M. H. Dominiczak, *Handbook of lipoprotein testing*. Amer. Assoc. for Clinical Chemistry, 2000.
[34] J. Lovrić, M. Mesić, M. Macan, M. Koprivanac, M. Kelava, and V. Bradamante, "Measurement of malondialdehyde (MDA) level in rat plasma after simvastatin treatment using two different analytical methods," *Periodicum biologorum,* vol. 110, no. 1, pp. 63-68, 2008.
[35] D. R. Matthews, J. P. Hosker, A. S. Rudenski, B. Naylor, D. F. Treacher, and R. C. Turner, "Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man," *diabetologia,* vol. 28, pp. 412-419, 1985.
[36] J. D. Bancroft and M. Gamble, *Theory and practice of histological techniques*. Elsevier health sciences, 2008.
[37] J. Liu *et al.*, "Perinatal bisphenol A exposure and adult glucose homeostasis: identifying critical windows of exposure," *PloS one,* vol. 8, no. 5, p. e64143, 2013.
[38] A. M. Morgan, S. S. El-Ballal, B. E. El-Bialy, and N. B. El-Borai, "Studies on the potential protective effect of cinnamon against bisphenol A-and octylphenol-induced oxidative stress in male albino rats," *Toxicology reports,* vol. 1, pp. 92-101, 2014.
[39] O. Takahashi and S. Oishi, "Testicular toxicity of dietary 2, 2-bis (4-hydroxyphenyl) propane (bisphenol A) in F344 rats," *Archives of toxicology,* vol. 75, pp. 42-51, 2001.

[40] V. Bindhumol, K. Chitra, and P. Mathur, "Bisphenol A induces reactive oxygen species generation in the liver of male rats," *Toxicology,* vol. 188, no. 2-3, pp. 117-124, 2003.
[41] M. Razzoli, P. Valsecchi, and P. Palanza, "Chronic exposure to low doses bisphenol A interferes with pair-bonding and exploration in female Mongolian gerbils," *Brain research bulletin,* vol. 65, no. 3, pp. 249-254, 2005.
[42] H. S. Aboul Ezz, Y. A. Khadrawy, and I. M. Mourad, "The effect of bisphenol A on some oxidative stress parameters and acetylcholinesterase activity in the heart of male albino rats," *Cytotechnology,* vol. 67, no. 1, pp. 145-155, 2015/01/01 2015, doi: 10.1007/s10616-013-9672-1.
[43] E. Hoque *et al.*, "Effects of bisphenol-A (BPA) on body weight, hematological parameters and histo-texture of kidney in swiss albino mice," *Asian Journal of Medical and Biological Research,* vol. 6, no. 4, pp. 635-640, 2020.
[44] N. Ben-Jonathan, E. R. Hugo, and T. D. Brandebourg, "Effects of bisphenol A on adipokine release from human adipose tissue: Implications for the metabolic syndrome," *Molecular and cellular endocrinology,* vol. 304, no. 1-2, pp. 49-54, 2009.
[45] M. K. Moon *et al.*, "Long-term oral exposure to bisphenol A induces glucose intolerance and insulin resistance," *J Endocrinol,* vol. 226, no. 1, pp. 35-42, 2015.
[46] I. Trouwborst, S. M. Bowser, G. H. Goossens, and E. E. Blaak, "Ectopic fat accumulation in distinct insulin resistant phenotypes; targets for personalized nutritional interventions," *Frontiers in nutrition,* vol. 5, p. 77, 2018.
[47] H. Kabuto, M. Amakawa, and T. Shishibori, "Exposure to bisphenol A during embryonic/fetal life and infancy increases oxidative injury and causes underdevelopment of the brain and testis in mice," *Life sciences,* vol. 74, no. 24, pp. 2931-2940, 2004.
[48] T. Kidani, S. Kamei, J. Miyawaki, J. Aizawa, K. Sakayama, and H. Masuno, "Bisphenol A downregulates Akt signaling and inhibits adiponectin production and secretion in 3T3-L1 adipocytes," *Journal of atherosclerosis and thrombosis,* vol. 17, no. 8, pp. 834-843, 2010.
[49] A. Durak, U. Gawlik-Dziki, and Ł. Pecio, "Coffee with cinnamon–Impact of phytochemicals interactions on antioxidant and anti-inflammatory in vitro activity," *Food chemistry,* vol. 162, pp. 81-88, 2014.
[50] C. L. Broadhurst, M. M. Polansky, and R. A. Anderson, "Insulin-like biological activity of culinary and medicinal plant aqueous extracts in vitro," *Journal of agricultural and food chemistry,* vol. 48, no. 3, pp. 849-852, 2000.
[51] S. H. Kim, S. H. Hyun, and S. Y. Choung, "Anti-diabetic effect of cinnamon extract on blood glucose in db/db mice," *Journal of ethnopharmacology,* vol. 104, no. 1-2, pp. 119-123, 2006.
[52] H. G. Preuss, B. Echard, M. M. Polansky, and R. Anderson, "Whole cinnamon and aqueous extracts ameliorate sucrose-induced blood pressure elevations in spontaneously hypertensive rats," *Journal of the American College of Nutrition,* vol. 25, no. 2, pp. 144-150, 2006.
[53] X. Xiang, "The use of cinnamic acid to prepare for antidiabetic medicine," *Paten number,* vol. 99115661, p. 7, 1999.
[54] Y. Shen *et al.*, "Verification of the antidiabetic effects of cinnamon (Cinnamomum zeylanicum) using insulin-uncontrolled type 1 diabetic rats and cultured adipocytes," *Bioscience, biotechnology, and biochemistry,* vol. 74, no. 12, pp. 2418-2425, 2010.
[55] P. Alonso-Magdalena, S. Morimoto, C. Ripoll, E. Fuentes, and A. Nadal, "The estrogenic effect of bisphenol A disrupts pancreatic β-cell function in vivo and induces insulin resistance," *Environmental health perspectives,* vol. 114, no. 1, pp. 106-112, 2006.
[56] A. Nadal, P. Alonso‐Magdalena, S. Soriano, A. B. Ropero, and I. Quesada, "The role of oestrogens in the adaptation of islets to insulin resistance," *The Journal of physiology,* vol. 587, no. 21, pp. 5031-5037, 2009.
[57] A. Nadal, A. B. Ropero, O. Laribi, M. Maillet, E. Fuentes, and B. Soria, "Nongenomic actions of estrogens and xenoestrogens by binding at a plasma membrane receptor unrelated to estrogen receptor α and estrogen receptor β," *Proceedings of the National Academy of Sciences,* vol. 97, no. 21, pp. 11603-11608, 2000.
[58] J. Fu *et al.*, "The impairment of glucose-stimulated insulin secretion in pancreatic β-cells caused by prolonged glucotoxicity and lipotoxicity is associated with elevated adaptive antioxidant response," *Food and chemical toxicology,* vol. 100, pp. 161-167, 2017.
[59] W. L. Baker, G. Gutierrez-Williams, C. M. White, J. Kluger, and C. I. Coleman, "Effect of cinnamon on glucose control and lipid parameters," *Diabetes care,* vol. 31, no. 1, pp. 41-43, 2008.

[60] J.-W. Hong, G.-E. Yang, Y. B. Kim, S. H. Eom, J.-H. Lew, and H. Kang, "Anti-inflammatory activity of cinnamon water extract in vivo and in vitro LPS-induced models," *BMC complementary and alternative medicine,* vol. 12, no. 1, pp. 1-8, 2012.

[61] J. Imparl-Radosevich *et al.*, "Regulation of PTP-1 and insulin receptor kinase by fractions from cinnamon: implications for cinnamon regulation of insulin signalling," *Hormone research,* vol. 50, no. 3, pp. 177-182, 1998.

[62] H. Ping, G. Zhang, and G. Ren, "Antidiabetic effects of cinnamon oil in diabetic KK-Ay mice," *Food and chemical toxicology,* vol. 48, no. 8-9, pp. 2344-2349, 2010.

[63] S. Kreydiyyeh, J. Usta, and R. Copti, "Effect of cinnamon, clove and some of their constituents on the Na+-K+-ATPase activity and alanine absorption in the rat jejunum," *Food and Chemical Toxicology,* vol. 38, no. 9, pp. 755-762, 2000.

[64] W. M. Ahmed, W. A. Moselhy, and T. Nabil, "Bisphenol A toxicity in adult male rats: hematological, biochemical and histopathological approach," *Global veterinaria,* vol. 14, no. 2, pp. 228-238, 2015.

[65] F. Furukawa *et al.*, "A 13-week subchronic toxicity study of bisphenol A in B6C3F1 mice," *Eisei Shikenjo hokoku. Bulletin of National Institute of Hygienic Sciences,* no. 112, pp. 89-96, 1994.

[66] T. Umano, K. Miyata, Y. Minobe, and K. Yamasaki, "Enhanced OECD TG 407 in detection of endocrine-mediated effects of 4, 4′-(octahydro-4, 7-methano-5H-inden-5-ylidene) bisphenol," *Archives of toxicology,* vol. 84, pp. 175-182, 2010.

[67] O. K. Ulutaş, N. Yıldız, E. Durmaz, M. A. Ahbab, N. Barlas, and İ. Çok, "An in vivo assessment of the genotoxic potential of bisphenol A and 4-tert-octylphenol in rats," *Archives of toxicology,* vol. 85, pp. 995-1001, 2011.

[68] K. Yamasaki and H. Okuda, "Comparison of endocrine-mediated effects of two bisphenol A related compounds, 2, 2-bis (4-cyanatophyenyl) propane and 4, 4′-cyclohexylidenebisphenol, based on subacute oral toxicity studies using rats," *Toxicology letters,* vol. 208, no. 2, pp. 162-167, 2012.

[69] P. Thomas, M. Bally, and J. Neff, "Ascorbic acid status of mullet, Mugil cephalus Linn., exposed to cadmium," *Journal of Fish Biology,* vol. 20, no. 2, pp. 183-196, 1982.

[70] A. Mahmoudi *et al.*, "Oleuropein and hydroxytyrosol rich extracts from olive leaves attenuate liver injury and lipid metabolism disturbance in bisphenol A-treated rats," *Food & function,* vol. 9, no. 6, pp. 3220-3234, 2018.

[71] S. Hassan *et al.*, "Phytochemical and toxicological studies of aqueous leaves extracts of Erythrophleum africanum," *Pakistan Journal of Biological Sciences: PJBS,* vol. 10, no. 21, pp. 3815-3821, 2007.

[72] K. Yamasaki, M. Sawaki, S. Noda, N. Imatanaka, and M. Takatsuki, "Subacute oral toxicity study of ethynylestradiol and bisphenol A, based on the draft protocol for the'Enhanced OECD Test Guideline no. 407'," *Archives of toxicology,* vol. 76, pp. 65-74, 2002.

[73] K. Yamasaki, M. Takeyoshi, S. Noda, and M. Takatsuki, "Changes of serum alpha2u-globulin in the subacute oral toxicity study of ethynyl estradiol and bisphenol A based on the draft protocol for the 'enhanced OECD test guideline No. 407'," *Toxicology,* vol. 176, no. 1-2, pp. 101-112, 2002.

[74] S. H. Vagvala and S. D. O'Connor, "Imaging of abnormal liver function tests," *Clinical liver disease,* vol. 11, no. 5, p. 128, 2018.

[75] S. Torabi, M. R. Asad, and A. Tabrizi, "The effect of endurance training with cinnamon supplementation on plasma concentrations of liver enzymes (ALT, AST) in women with type II diabetes," *Tehran University of Medical Sciences Journal,* vol. 74, no. 6, pp. 433-441, 2016.

[76] A. Ghonim *et al.*, "Protective effect of cinnamon against cadmium-induced hepatorenal oxidative damage in rats," *Int J Pharmacol Toxicol,* vol. 5, no. 1, pp. 17-22, 2017.

[77] T. Geetharathan and P. Josthna, "Effect of BPA on protein, lipid profile and immuno-histo chemical changes in placenta and uterine tissues of albino rat," *International Journal of Pharmaceutical and Clinical Research,* vol. 8, no. 4, pp. 260-268, 2016.

[78] M. K. Moon *et al.*, "Bisphenol A impairs mitochondrial function in the liver at doses below the no observed adverse effect level," *Journal of Korean medical science,* vol. 27, no. 6, pp. 644-652, 2012.

[79] R. L. Bertholf, "Proteins and albumin," *Laboratory Medicine,* vol. 45, no. 1, pp. e25-e41, 2014.

[80] K. Chitra, C. Latchoumycandane, and P. Mathur, "Induction of oxidative stress by bisphenol A in the epididymal sperm of rats," *Toxicology,* vol. 185, no. 1-2, pp. 119-127, 2003.

[81] H. G. Abdel-Rahman, H. Abdelrazek, D. W. Zeidan, R. M. Mohamed, and A. M. Abdelazim, "Lycopene: hepatoprotective and antioxidant effects toward bisphenol A-induced toxicity in female Wistar rats," *Oxidative medicine and cellular longevity,* vol. 2018, , Article ID 5167524, 8 pages, 2018.

[82] G. E. Elshopakey and S. T. Elazab, "Cinnamon aqueous extract attenuates diclofenac sodium and oxytetracycline mediated hepato-renal toxicity and modulates oxidative stress, cell apoptosis, and inflammation in male albino rats," *Veterinary Sciences,* vol. 8, no. 1, p. 9, 2021.

[83] A. Eidi, P. Mortazavi, M. Bazargan, and J. Zaringhalam, "Hepatoprotective activity of cinnamon ethanolic extract against CCI4-induced liver injury in rats," *Excli Journal,* vol. 11, p. 495, 2012.

[84] A. Kobroob, W. Peerapanyasut, N. Chattipakorn, and O. Wongmekiat, "Damaging effects of bisphenol A on the kidney and the protection by melatonin: Emerging evidences from in vivo and in vitro studies," *Oxidative medicine and cellular longevity,* vol. 2018, Article ID 3082438, 15 pages, 2018.

[85] J. Treasure, "Urtica semen reduces serum creatinine levels," *J Am Herbal Guild,* vol. 4, no. 2, pp. 22-25, 2003.

[86] M. A. Dollah, S. Parhizkar, and M. Izwan, "Effect of Nigella sativa on the kidney function in rats," *Avicenna journal of phytomedicine,* vol. 3, no. 2, p. 152, 2013.

[87] D. K. Weber, K. Danielson, S. Wright, and J. E. Foley, "Hematology and serum biochemistry values of dusky-footed wood rat (Neotoma fuscipes)," *Journal of Wildlife Diseases,* vol. 38, no. 3, pp. 576-582, 2002.

[88] E. Lusiana, N. Tamzil, and D. Oktarina, "Efficacy of cinnamon (Cinnamomum burmannii) extract to decrease serum creatinine in acute kidney injury induced male wistar rats," *Bioscientia Medicina : Journal of Biomedicine and Translational Research,* vol. 3, p. 29, 10/27 2019, doi: 10.32539/bsm.v3i4.101.

[89] E. Lusiana, N. S. Tamzil, and D. Oktarina, "The Efficacy of Cinnamon Extract (Cinnamomum burmannii) on Reducing Staging Acute Kidney Injury in Ischemia Reperfusion (IR) Model," *Bioscientia Medicina: Journal of Biomedicine and Translational Research,* vol. 5, no. 2, pp. 200-203, 2021.

[90] D. R. A. Muhammad, E. Tuenter, G. D. Patria, K. Foubert, L. Pieters, and K. Dewettinck, "Phytochemical composition and antioxidant activity of Cinnamomum burmannii Blume extracts and their potential application in white chocolate," *Food Chemistry,* vol. 340, p. 127983, 2021.

[91] A. Marmugi *et al.*, "Adverse effects of long-term exposure to bisphenol A during adulthood leading to hyperglycaemia and hypercholesterolemia in mice," *Toxicology,* vol. 325, pp. 133-143, 2014.

[92] G. Robertson, I. Leclercq, and G. C. Farrell, "II. Cytochrome P-450 enzymes and oxidative stress," *American Journal of Physiology-Gastrointestinal and Liver Physiology,* vol. 281, no. 5, pp. G1135-G1139, 2001.

[93] J. S. Johansen, A. K. Harris, D. J. Rychly, and A. Ergul, "Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice," *Cardiovascular diabetology,* vol. 4, no. 1, pp. 1-11, 2005.

[94] L. Lacoste, J. Y. Lam, J. Hung, G. Letchacovski, C. B. Solymoss, and D. Waters, "Hyperlipidemia and coronary disease: correction of the increased thrombogenic potential with cholesterol reduction," *Circulation,* vol. 92, no. 11, pp. 3172-3177, 1995.

[95] C. S. Watson, Y.-J. Jeng, and M. Y. Kochukov, "Nongenomic signaling pathways of estrogen toxicity," *Toxicological sciences,* vol. 115, no. 1, pp. 1-11, 2010.

[96] A. Khan, M. Safdar, M. M. Ali Khan, K. N. Khattak, and R. A. Anderson, "Cinnamon improves glucose and lipids of people with type 2 diabetes," *Diabetes care,* vol. 26, no. 12, pp. 3215-3218, 2003.

[97] F. N. Alsoodeeri, H. M. Alqabbani, and N. M. Aldossari, "Effects of cinnamon (Cinnamomum cassia) consumption on serum lipid profiles in albino rats," *Journal of lipids,* vol. 2020, , Article ID 8469830, 7 pages, 2020.

[98] J.-S. Lee *et al.*, "Cinnamate supplementation enhances hepatic lipid metabolism and antioxidant defense systems in high cholesterol-fed rats," *Journal of medicinal food,* vol. 6, no. 3, pp. 183-191, 2003.

[99] P. S. Babu, S. Prabuseenivasan, and S. Ignacimuthu, "Cinnamaldehyde—a potential antidiabetic agent," *Phytomedicine,* vol. 14, no. 1, pp. 15-22, 2007.

[100] U. K. Patil, S. Saraf, and V. Dixit, "Hypolipidemic activity of seeds of Cassia tora Linn," *Journal of ethnopharmacology,* vol. 90, no. 2-3, pp. 249-252, 2004.

[101] S. Kannappan, T. Jayaraman, P. Rajasekar, M. Ravichandran, and C. Anuradha, "Cinnamon bark extract improves glucose metabolism and lipid profile in the fructose-fed rat," *Singapore medical journal,* vol. 47, no. 10, p. 858, 2006.

[102] S. E. S. Elswefy, F. R. Abdallah, H. H. Atteia, A. S. Wahba, and R. A. Hasan, "Inflammation, oxidative stress and apoptosis cascade implications in bisphenol A-induced liver fibrosis in male rats," *International journal of experimental pathology,* vol. 97, no. 5, pp. 369-379, 2016.

[103] H. Abdelrazek, D. A. Eltamany, M. T. Soliman, S. M. Greish, and H. M. Ebaid, "Effect of Lycopene on Bisphenol A-induced Immunological Disturbances in Albino Male Rats," *Suez Canal University Medical Journal,* vol. 22, no. 1, pp. 9-17, 2019.

[104] H. A. Edres, N. M. Taha, A. Mandour, and M. A. Lebda, "Impact of L-carnitine on bisphenol A-induced kidney damage in rats," *Alexendrai Journal of Veterinary Sciences*, vol. 56, no.1, pp. 11-17, 2018.

[105] E. Yalçın, K. Çavuşoğlu, A. Acar, and K. Yapar, "In vivo protective effects of Ginkgo biloba L. leaf extract against hydrogen peroxide toxicity: cytogenetic and biochemical evaluation," *Environmental Science and Pollution Research,* vol. 27, pp. 3156-3164, 2020.
[106] G. Das *et al.*, "Cardiovascular protective effect of cinnamon and its major bioactive constituents: An update," *Journal of Functional Foods,* vol. 97, p. 105045, 2022.
[107] C. Zhu, H. Yan, Y. Zheng, H. O. Santos, M. S. Macit, and K. Zhao, "Impact of cinnamon supplementation on cardiometabolic biomarkers of inflammation and oxidative stress: a systematic review and meta-analysis of randomized controlled trials," *Complementary therapies in medicine,* vol. 53, p. 102517, 2020.
[108] S. Vetal, S. L. Bodhankar, V. Mohan, and P. A. Thakurdesai, "Anti-inflammatory and anti-arthritic activity of type-A procyanidine polyphenols from bark of Cinnamomum zeylanicum in rats," *Food Science and Human Wellness,* vol. 2, no. 2, pp. 59-67, 2013.
[109] R. A. Elgawish, M. A. El-Beltagy, R. M. El-Sayed, A. A. Gaber, and H. M. Abdelrazek, "Protective role of lycopene against metabolic disorders induced by chronic bisphenol A exposure in rats," *Environmental Science and Pollution Research,* vol. 27, pp. 9192-9201, 2020.
[110] F. Ariemma *et al.*, "Low-dose bisphenol-A impairs adipogenesis and generates dysfunctional 3T3-L1 adipocytes," *PloS one,* vol. 11, no. 3, p. e0150762, 2016.
[111] A. Ahangarpour, G. Afshari, S. A. Mard, A. Khodadadi, and M. Hashemitabar, "Alteration effect of Exendin-4 on oxidative stress and metabolic disorders induced by Bisphenol A in adult male mice," *Jentashapir Journal of Health Research,* vol. 7, no. 5, pp. 1-6. 2016.
[112] D. Zieba, W. Biernat, and J. Barć, "Roles of leptin and resistin in metabolism, reproduction, and leptin resistance," *Domestic animal endocrinology,* vol. 73, p. 106472, 2020.
[113] R. Naomi *et al.*, "Bisphenol A (BPA) leading to obesity and cardiovascular complications: a compilation of current in vivo study," *International journal of molecular sciences,* vol. 23, no. 6, p. 2969, 2022.
[114] M.-J. Lee, Y. Wu, and S. K. Fried, "Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications," *Molecular aspects of medicine,* vol. 34, no. 1, pp. 1-11, 2013.
[115] N. Esser, S. Legrand-Poels, J. Piette, A. J. Scheen, and N. Paquot, "Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes," *Diabetes research and clinical practice,* vol. 105, no. 2, pp. 141-150, 2014.
[116] A. J. Blanca *et al.*, "Leptin induces oxidative stress through activation of nadph oxidase in renal tubular cells: antioxidant effect of L-Carnitine," *Journal of cellular biochemistry,* vol. 117, no. 10, pp. 2281-2288, 2016.
[117] G. Raghuraman, M. C. Zuniga, H. Yuan, and W. Zhou, "PKCε mediates resistin-induced NADPH oxidase activation and inflammation leading to smooth muscle cell dysfunction and intimal hyperplasia," *Atherosclerosis,* vol. 253, pp. 29-37, 2016.
[118] G. Fantuzzi and R. Faggioni, "Leptin in the regulation of immunity, inflammation, and hematopoiesis," *Journal of leukocyte biology,* vol. 68, no. 4, pp. 437-446, 2000.
[119] S. Hurrle and W. H. Hsu, "The etiology of oxidative stress in insulin resistance," *Biomedical journal,* vol. 40, no. 5, pp. 257-262, 2017.
[120] M. Mostafazadeh, S. Haiaty, A. Rastqar, and M. Keshvari, "Correlation between resistin level and metabolic syndrome component: a review," *Hormone and Metabolic Research,* vol. 50, no. 07, pp. 521-536, 2018.
[121] M. Sfar *et al.*, "Effect of cinnamon supplementation on resistin and ghrelin in obese diabetic men," *Indian Journal of Traditional Knowledge (IJTK),* vol. 18, no. 4, pp. 694-701, 2019.
[122] J. M. Friedman, "Leptin and the regulation of body weight," *Harvey lectures,* vol. 95, pp. 107-136, 1999.
[123] A. Khan, N. A. Bryden, M. M. Polansky, and R. A. Anderson, "Insulin potentiating factor and chromium content of selected foods and spices," *Biological trace element research,* vol. 24, pp. 183-188, 1990.
[124] A. Sangal, "Role of cinnamon as beneficial antidiabetic food adjunct: a review," *Advances in Applied Science Research,* vol. 2, no. 4, pp. 440-450, 2011.
[125] K. Couturier *et al.*, "Cinnamon increases liver glycogen in an animal model of insulin resistance," *Metabolism,* vol. 60, no. 11, pp. 1590-1597, 2011.
[126] S. Adisakwattana, O. Lerdsuwankij, U. Poputtachai, A. Minipun, and C. Suparpprom, "Inhibitory activity of cinnamon bark species and their combination effect with acarbose against intestinal α-glucosidase and pancreatic α-amylase," *Plant Foods for Human Nutrition,* vol. 66, pp. 143-148, 2011.
[127] A. H. Haghighi, H. Yarahmadi, A. Ildarabadi, and A. Rafieepour, "The effect of aerobic training on serum levels of ghrelin and leptin in middle-aged men," *Daneshvar Medicine,* vol. 19, no. 6, pp. 79-90, 2012.

[128] K. Moriyama *et al.*, "Thyroid hormone action is disrupted by bisphenol A as an antagonist," *The Journal of Clinical Endocrinology & Metabolism,* vol. 87, no. 11, pp. 5185-5190, 2002.

[129] H. Sun, O.-X. Shen, X.-R. Wang, L. Zhou, S.-q. Zhen, and X.-d. Chen, "Anti-thyroid hormone activity of bisphenol A, tetrabromobisphenol A and tetrachlorobisphenol A in an improved reporter gene assay," *Toxicology in vitro,* vol. 23, no. 5, pp. 950-954, 2009.

[130] K.-W. Kong, N. F. Rajab, K. N. Prasad, A. Ismail, M. Markom, and C.-P. Tan, "Lycopene-rich fractions derived from pink guava by-product and their potential activity towards hydrogen peroxide-induced cellular and DNA damage," *Food chemistry,* vol. 123, no. 4, pp. 1142-1148, 2010.

[131] T. G. Gaique, B. P. Lopes, L. L. Souza, G. S. Paula, C. C. Pazos‐Moura, and K. J. Oliveira, "Cinnamon intake reduces serum T3 level and modulates tissue‐specific expression of thyroid hormone receptor and target genes in rats," *Journal of the Science of Food and Agriculture,* vol. 96, no. 8, pp. 2889-2895, 2016.

[132] B. P. Lopes *et al.*, "Beneficial effects of Cinnamon on hepatic lipid metabolism are impaired in hypothyroid rats," *Journal of functional foods,* vol. 50, pp. 210-215, 2018.

[133] P. E. Macchia *et al.*, "Increased sensitivity to thyroid hormone in mice with complete deficiency of thyroid hormone receptor alpha," (in eng), *Proc Natl Acad Sci U S A,* vol. 98, no. 1, pp. 349-54, Jan 2 2001, doi: 10.1073/pnas.98.1.349.

[134] M. A. S. Amin, H. M. A. Sonpol, R. H. E. Gouda, and A. M. Aboregela, "Bisphenol A enhances apoptosis, fibrosis, and biochemical fluctuations in the liver of adult male rats with possible regression after recovery," (in eng), *Anatomical record (Hoboken, N.J. : 2007),* vol. 306, no. 1, pp. 213-225, Jan 2023, doi: 10.1002/ar.25032.

[135] M. Nagarajan, G. B. Maadurshni, and J. Manivannan, "Exposure to low dose of Bisphenol A (BPA) intensifies kidney oxidative stress, inflammatory factors expression and modulates Angiotensin II signaling under hypertensive milieu," vol. 38, no. 1, p. e23533, 2024, doi: https://doi.org/10.1002/jbt.23533.

[136] T. Iqbal, R. Yasmeen, and F. J. B. Hafeez, "Effectiveness of Cinnamomum cassia against liver and kidney biochemical assay and hematology in bisphenol-a induced rats," vol. 69, no. 1, pp. 7-14, 2023.

[137] O. E. Ola-Davies and S. G. Olukole, "Gallic acid protects against bisphenol A-induced alterations in the cardio-renal system of Wistar rats through the antioxidant defense mechanism," *Biomedicine & Pharmacotherapy,* vol. 107, pp. 1786-1794, 2018/11/01/ 2018, doi: https://doi.org/10.1016/j.biopha.2018.08.108.

[138] P. Nuñez, J. Arguelles, and C. Perillan, "Effects of short-term exposure to low doses of bisphenol A on cellular senescence in the adult rat kidney," *Histochemistry and Cell Biology,* vol. 159, no. 5, pp. 453-460, 2023/05/01 2023, doi: 10.1007/s00418-022-02178-x.

[139] A. M. Morgan, S. S. El-Ballal, B. E. El-Bialy, and N. B. El-Borai, "Studies on the potential protective effect of cinnamon against bisphenol A- and octylphenol-induced oxidative stress in male albino rats," *Toxicology Reports,* vol. 1, pp. 92-101, 2014/01/01/ 2014, doi: https://doi.org/10.1016/j.toxrep.2014.04.003.